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EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1643

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/852,547	SIRBASKU, DAVID A.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☐ Claim(s) 1-8, 12-15, 17-20, 66-69, 71, 73-79, 81-90 and 92-94 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-8, 12-15, 17-20, 66-69, 71, 73-79, 81-90 and 92-94 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. ____   |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date ____  | 6) <input type="checkbox"/> Other: ____                                     |

Art Unit: 1643

### **DETAILED ACTION**

Claim 91 has been canceled. Claim 18 has been amended. Claims 1-8, 12-15, 17-20, 66-69, 71, 73-79, 81-90 and 92-94 are pending and under consideration.

Sections of Title 35, U.S. Code, not found in this action, can be found in a prior action.

Claim 91 has been canceled. Claim 18 has been amended. Claims 1-8, 12-15, 17-20, 66-69, 71, 73-79, 81-90 and 92-94 are pending and under consideration.

Sections of Title 35, U.S. Code, not found in this action, can be found in a prior action.

The rejection of claims 1-6, 12, 17-19, 66, 67, 70, 73-76 and 81-86 and 89 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. New claim 94 is also rejected for the reasons of record below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claims 1-6, 12, claim 17 in part, 18 in part, 19 in part, 66, 67, 70, 73-76 and 81-86, 89 and 91 are rejected under 112, first lack of enablement for quantitating or detecting an immunoglobulin inhibitor of steroid hormone responsive cell growth in a specimen of body fluid or secretion. the specification states on page 10, [0018] that for "purpose of this disclosure, the term "immunoglobulin inhibitor" refers to a secretory immunoglobulin, preferably on of the secretory immunoglobulins IgA, IgM and Ig1 that is active for inhibiting proliferation of a steroid hormone responsive cancer cell. The specification bases the instant claims on the premise that measurement of said secretory immunoglobulins would then be diagnostic for inhibition of steroid responsive cell growth and that decreased levels of said immunoglobulins would then be indicative of decreased inhibition of said cell growth. The specification teaches that the secretory immunoglobulin system decreases activity with age. This is a general teaching dependent upon the averaging of multiple measurements of secretory immunoglobulins over a period of time encompassing years. However, it is known in the art that levels of IgA, the major

Art Unit: 1643

secretory immunoglobulin, vary as a function of time of day, as well as within a year, and large variations between healthy subjects is documented (Garde et al, Clinical Chemistry, 2000, Vol. 46, pp. 551-559, cited in a previous action). The art also teaches that levels of secretory IgA is hormonally regulated in women and thus variable over the course of a menstrual cycle (Gomez et al, Amer J Reproduc Immunol, 1993, Vol. 29, pp. 219-223, cited in a previous action). It would be reasonable to conclude that the level of the other types of secretory immunoglobulins would also vary as a function of the exposure of an individual to exogenous antigens or substances provoking an immune reaction. Thus, it would be reasonable to conclude that the measurement of secretory immunoglobulins in a single sample would not be representative of the average level of secretory immunoglobulins present within an individual during the course of a year or more. Given that the art teaches that the level of IgA, the major secretory immunoglobulin, varies both positively and negatively with time in a healthy individual and also varies between individual subjects and thus supports the conclusion that the level of other secretory immunoglobulins also vary with time by both increasing and decreasing; and given the lack of teachings in the specification regarding ranges or levels of secretory immunoglobulins that were indicative of normal individual versus individuals having a steroid hormone responsive cancer, one of skill in the art would be subject to undue experimentation in order to make and use the claimed methods relying on correlating the levels of secretory immunoglobulins with the presence or susceptibility to steroid hormone responsive cancer. Further, Sullivan et al (Immunology, 1983, Vol. 49, pp. 379-386) observe that the transudation of IgA in the uterus is mediated through the hormonal control of secretory component (page 380, first column, lines 23-29), but that the estradiol accumulation of secretory component appears to be independent of IgA, because of the demonstration that dexamethasone suppressed IgA accumulation but not secretory protein accumulation (page 379, first column, lines 14-18). Notably, Sullivan et al state that following estradiol treatment, the source of uterine IgG appears to be plasma.

Hurlimann et al (Virchows Arch A Path Anat and Histol, 1978, Vol. 377, pp. 211-223) observe that in human biopsies of the endometrium that the endometrium did not synthesize immunoglobulins; secretory component was synthesized only by endometrial tissue in the secretory phase and by some carcinomas (Summary, lines 13-16). Hurlimann et al observe that there is no relationship between the production of secretory component and the presence of IgA

Art Unit: 1643

plasmacytes which localize as a result of immunologic influences within the tissues studied (summary, lines 16-19). Hurlimann et al disclose that in cervical tissues without a pathologic lesion exhibited few plasmacytes around glands and under the surface epithelium, and that culturing of the samples in vitro led to the identification of a very low level of synthesized immunoglobulins within the tissue (page 213, under the heading "Cervical Tissues without Lesion"). Hurlimann et al disclose that a low level of immunoglobulin synthesis could be detected by the culturing of neoplastic cervical tissue and that said tissue also showed few plasmacytes (page 214, under the heading of "Cervical Tissues with Metaplasia", in contrast to cervical neoplasia where the synthesis of IgG and IgA was marked and correlated with the presence of numerous IgG and IgA plasmacytes (page 215-216, under the heading "Carcinoma in Situ"). Hurlimann et al disclose that in the culturing of endometrial carcinoma biopsy samples the numerous IgG plasmacytes demonstrated immunoglobulin synthesis (page 219, under the heading of "Carcinoma"). Hurlimann et al conclude that secretory component is synthesized in excess when compared to the synthesis of IgA (page 219, lines 18-21 under the heading "Discussion"). Hurlimann et al disclose that although IgA synthesis in the samples examined is decreased in the age group between 44-68 years, loss of IgA synthesis is replaced by IgG synthesis (page 219, lines 27-35, under the heading of "Discussion"). Thus, it can be concluded that the transcytosis of secretory immunoglobulin is dependent upon the presence of local plasmacytes or the presence of an immunoglobulin in the serum. Further, Fudenberg et al (Basic and Clinical Immunology, 1978, page 326, pp. 324-328) teach that overall serum concentrations of IgG and IgA tend to increase with age whereas serum IgM tends to decrease (especially, page 326, second column, lines 9-10). Therefore, one of skill in the art would not conclude that persons of advancing age were deficient in IgG or IgA in serum levels, or IgG in mucosal levels.

Richarson et al (Journal of Steroid Biochemistry and Molecular Biology, 1993, Vol. 47, pp. 143-149) disclose that IL-6 and IFN-gamma in conjunction with estrogen resulted in an increase of both secretory component and IgA levels in uterine secretions in rat uteri and concluded that the regulation of secretory component is complex because it is controlled by the interactions of cytokines and sex hormones through both autocrine and paracrine effects (page 132, second column, lines 12-22). Brandtzaeg et al (In: Developments in Biological Standardization, Brown and Haaheim, Ed.s, March 1998, Vol. 92, pp. 93-108) teach that secretory

Art Unit: 1643

component can be up-regulated by IFN-gamma, Il-4 and TNF-alpha (pages 95-96, bridging sentence) which corroborates the teachings of Richardson et al. Verrijdt et al (Biochem Soc Transactions, 1997 May, Vol. 25, page 186S) report that human secretory component gene expression is under the influence of TNF-alpha, IFN-gamma, TGF-beta, glucocorticoids, estrogens and androgens, but the influence of estrogen appears to be opposed in the mammary gland and in the uterus (column 1, first paragraph). It is noted that the instant claims are broadly drawn to encompass any type of epithelial cancer, not just breast, and any type of steroid hormone response, not just a response to estrogen, and that the response to estrogen is a function of the tissue type.

Tamiolakis et al (European Journal of Gynaecological Oncology, 2002, Vol. 23, pp. 453-456) discloses that the expression of secretory component increases as endometrial hyperplasia progresses to endometrial carcinoma (page 455, second column, last sentence). One of skill in the art would reasonably conclude that the transudation of immunoglobulins would be increased as a result of the progression to cancer, because there is more secretory component available to transcytosis any available immunoglobulin.

Klein et al (Journal of the National Cancer Institute, 1978, Vol. 61, pp. 57-60) teaches that the level of free secretory component increased dramatically in mucinous cyst fluid and ovarian carcinomas and in particularly mucinous adenocarcinomas (page 58, first two paragraphs under the heading of "results"). One of skill in the art would reasonably conclude that the transudation of immunoglobulins by these tissues would be increased because there is more secretory component available to transcytosis any available immunoglobulin. Garcia et al (American Journal of Obstetrics and Gynecology, 1977, Vol. 129, pp. 281-284) report that effusions from 12 epithelial tumor of the ovary comprises IgG, IgM and IgA, whereas in non-cancerous ovarian tissue, only IgG was detected (abstract, lines 1-6). One of skill in the art would reasonably conclude that the tumors were associated with IgM as well as IgA. Garcia et al teach that free secretory component was detected in all malignant and benign samples, therefore the tumor had not lost the ability to transcytose immunoglobulins.

Thalman et al (American Journal of Obstetrics and Gynecology, 1979, Vol. 134, pp. 899-903) teach that increased secretory component is detected in the plasma of patients with tumors of the colon, lung, breast, bladder and ovary (page 899, column 1, lines 9-11). It can be

Art Unit: 1643

reasonably concluded that the tumor is the source of the increase in free secretory component, therefore said tumor would be able to transcytose immunoglobulins from serum or local plasmacytes.

Given the above teaching of the prior art, one of skill would reasonably conclude that in or around epithelial tumors the local levels of immunoglobulins are increased or at the same level as in normal tissue. One of skill in the art would also conclude that secretory component is up-regulated in tumors relative to normal tissues and that the increase in secretory component associated with tumorigenesis would imply an increase transcytosis of available immunoglobulins. It would also be reasonably concluded in light of the teachings of Tamiolakis et al that pre-neoplastic cells would exhibit an intermediate level of secretory component expression and therefore would exhibit an intermediate level of transcytosis. Further, the teachings of Hurlimaan and Fudenberg do not support an overall decrease in immunoglobulins available for transcytosis by the secretory component. One of skill in the art would not be able to use the instant methods because they are contrary to the observations in the art, that levels of immunoglobulins in the vicinity of epithelial tumors do not decline, and in some cases are increased relative to normal tissue.

Applicant argues that the specification is enabling and points out examples 22 and 23. These examples have been considered but not found persuasive. Within example 22 it is stated:

*[0635] To determine if IgA/IgM responsive cells expressed 1000 kDa poly-Ig receptor, the Western analysis shown in FIG. 116 was done. Amounts of extracts of the designated cell types were analyzed with a 1:1000 dilution of rabbit anti-human secretory component. As expected MDCK cells were positive. This cell line has been studied for several years as a model of poly-Ig receptor sorting and function. LNCaP cells showed the same receptor (FIG. 116). Cell lines that were negative were ALVA-41, DU145, human fibroblasts, and PC3 cells (FIG. 116). As shown in multiple experiments described herein, LNCaP cells are IgA/IgM inhibited. The results of the Western analyses show that they express the poly-Ig receptor.*

*[0636] In the final experiments of this series, pIgA was tested with two of the cell lines that were poly-Ig receptor negative by the Western analysis shown in FIG. 116. The results with DU145 cells are shown in FIG. 117. Plasma IgA was not an inhibitor. A similar study with PC3 cells is*

Art Unit: 1643

*shown in FIG. 118. Again, pIgA was not an inhibitor even at 50 g/mL. These results demonstrate cells that lack the poly-Ig receptor are also insensitive to pIgA.*

*[0637] The HT-29 colon cancer cells are known to express only the authentic form of the poly-Ig receptor. They are also negatively growth regulated by IgM (FIG. 103). This implies that the poly-Ig receptor has more function than transcytosis only. This is very strong evidence in favor of the authentic poly-Ig receptor having a heretofore unrecognized growth regulating function in early stage cancers of colon. The HT-29 colon cancer cells are the source of a cDNA sequence for the poly-Ig receptor deposited in GENBANK. This sequence, hereby incorporated herein by reference, is very often referred to in published reports and shown to be equal to the exons identified from normal human leukocytes that were the source of the genomic sequence of the poly-Ig receptor. Taken together, all of the available data indicate that the authentic poly-Ig receptor has a new function, as identified and described herein.*

Under example 23 it is stated

*0652] The subclasses of human IgG are IgG1, IgG2, IgG 3 and IgG4. They are formed with both .lambda. and .kappa. light chains. A series of studies was performed, and it was found that with human breast cancer cells, only IgG1.kappa. was a significant estrogen reversible inhibitor. FIG. 120 shows a comparison of its activity to human pIgA and pIgM. At 40 .mu.g/mL, it was 37% as effective as pIgM. A similar study with LNCaP cells showed that only IgG1.kappa. had activity greater than the estrogenic effect seen in CAPM serum-free defined medium only (FIG. 121). However, in some experiments with prostate cells, IgG2K also showed androgen reversible inhibitory activity (FIG. 122). Based on these studies, it is concluded that IgG1 and IgG2 have small but measurable androgen reversible activity with AR.sup.+ human prostate cancer cells.*

The examples provide only information obtained in vitro with cell lines and do not address the lack of enablement issues with respect to a specimen of bodily fluids or secretions for predicting susceptibility to cancer.



Art Unit: 1643

Applicant requests that the examiner "file an affidavit for the record" to support the lack of enablement rejection or withdraw the rejection. Applicant is reminded that the MPEP makes no provision for the filing of an affidavit by an examiner. Applicant argues on page 15 of the response that the invention is described with sufficient detail to support a claim to showing the details of a method for predicting susceptibility of a subject to the development or growth of a steroid hormone responsive cancer as set forth the extensive survey of known cancers in Table 1. This has been considered but not found persuasive. Only cell lines are included in table 1, there are no examples of assaying a specimen of bodily fluids or secretions in Table 1.

Regarding paragraph 4 and the lack of a citation referring to a mucosal cancer, it is unclear what applicant is referring to. All the paragraph under the 112m 1st rejection for lacking enablement contain a citation.

Applicant continually argues that in "this unique microenvironment" the correlation of predictability can be made. However, this appears to be only speculation, as the specification provides no objective evidence that specimens of bodily fluids or secretions will reflect what is found in vitro in culture systems. There is no objective evidence that the "unique microenvironments" will provide a sample that will be different from any other sample of bodily fluid or secretion. Applicant is invited to provide a declaration setting forth scientific evidence to corroborate the instant claims as dictated by the MPEP (716).

Claims 7, 8, 13, 14, 17, 19, 20, 67, 68, 69, 77-79, 88, 92 and 93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to inadequate description of a genus

Claims 8, 9, 10, 11, 13, 14, 17, 19, 67, 72, 80 and 88 contain the limitations of "mediator of immunoglobulin inhibition of steroid hormone responsive cell growth". "defective mediator of immunoglobulin inhibition of steroid hormone responsive cell growth", "a poly-Ig receptor" "an

Art Unit: 1643

Fc receptor" , a "variant Fcgamma receptor", and "altered domain in said poly Ig receptor". The specification states on page 11[0022] that "certain other embodiments of the invention provide a method of detecting a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth that includes detecting a poly-Ig receptor". Thus, claims drawn to an immunoglobulin inhibitor of cell growth comprises a genus of inhibitors which include a poly-Ig receptor but is not limited only to poly-Ig receptors. further, given that the claim limitations require the determination of mediation of inhibition of steroid hormone cell growth , it is concluded that claims drawn to poly-Ig receptors and Fc receptors encompass defective and variant receptors which differ in amino acid sequence and function from the wild type receptors.

The instant method claims rely on the identity of variant poly-Ig, variant Fcgamma receptors, variant TGF-beta and genes. The claims are thus drawn to a genus of molecules encompassing mutant, truncated and otherwise variant poly-Ig, Fc receptor proteins and TGF-beta. The claims do not limit the "defect" in terms of specific structural or specific functional characteristics., thus it is not possible to determine if a given protein is member of the claimed genus. The specification does not teach a representative number of defective poly-Ig receptors or defective Fc receptors that would be representative of the claimed genus. Because the genres are highly variant, reliance on a description of the wild-type poly-Ig receptor or the Fcgamma receptor or the wild-type TGF-beta is insufficient to anticipate the claimed genus. The specification provides no teachings regarding DNA sequence or the protein encoded therefrom for any of the aforesaid variants or alleles of the poly Ig receptor or the Fc receptor. Claims 20, 77-79 and 93 are method claims relying on the identity of an "estrogen binding activity having a greater E2 binding affinity than that of ERalpha or ERbeta. The specification does not provide any structural information about said activity, and therefore lacks written description of said "activity".

Although drawn to DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. V. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical

Art Unit: 1643

species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. *Id.* At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.* Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. V. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product. Thus, the instant specification may provide an adequate written description of variants,

Art Unit: 1643

per Lilly by structurally describing a representative number of variants which negatively influence the inhibition of steroid hormone responsive cell growth or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus.". Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the steroid hormone/steroid hormone receptor, the defective poly-Ig receptor, the defective Fc receptors or the alternative alleles of the poly-Ig receptors, Fc receptor or TGF-beta to practice the methods of the instant invention in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete or partial structure or physical or chemical structure of the variants or alleles, nor any physical or chemical characteristics coupled with a known or disclosed correlation between structure and function. Regarding alleles and defective gene sequences, the specification does not identify said variant gene sequences. The general knowledge and skill in the art concerning alleles is that the structure of one allele is not representative of other unknown alleles. The same can be said of mutant genes, such as those encoding "defective" poly Ig receptor and defective Fc receptors. thus, the nature of both alleles and defective Fc receptors and defective poly Ig receptors is that they are variant structures and the in the present state of the art, the structure of one does not provide guidance for the structure of other s. The common attributes of the genus are not described. Thus, it is concluded that the specification does not provide a description of the disclosed steroid hormone receptor, variant poly-Ig receptors, variant Fc-receptors or alleles of TGF-beta that would satisfy the standard set out in Enzo.

Thus, the specification does not provide an adequate written description of the defective poly Ig receptors, defective Fc receptors, steroid hormone receptors, alleles participating in the allelic imbalance of poly-Ig receptors, Fc gamma receptors or TGF-beta receptor, required for the practice of the instant method claims. Since the specification fails to adequately describe disclosed immunoglobulin inhibitor, "a" poly Ig receptor or "a" Fc receptor and steroid hormone/steroid hormone receptor, it also fails to adequately describe the method reliant upon said products.

Art Unit: 1643

(B) As drawn to new matter

Claims 17, 19, 20, 77-79, 86 and 93 are rejected for the incorporation of new matter. Claim 17 has been amended to incorporate the limitation “a deletion of one or more of said second set of conditions indicating early onset of said cancerous or precancerous lesions”. Claim 19 has been amended to incorporate the limitation “the presence of one or more conditions from step (c) is further indicative of at least some degree of reduced prognosis”. Claim 20 has been amended to recite the limitations “indicating an estrogen-based therapy” and “contra-indicating an estrogen based therapy for treating said cancer”. Claim 93 has incorporated the limitation “the ability of said poly-Ig receptor to bind to the Fc domain of dimeric/polymeric IgA or polymeric IgM further indicates a therapy for treating said cancer”. The specification as filed lacks adequate written description for the amended claims. Applicant has not pointed out by page and line number the location in the specification which provides support for this amendment.

Applicant states that a genus/species relationship is a highly subjective determination more properly addressed with a restriction requirement. First, applicant is reminded of the written description requirement of 112, first paragraph. The MPEP (2163)II3(a) states

For each claim drawn to a genus:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Thus, the genus/species relationship is germane to the written description requirement.

Art Unit: 1643

Applicant argues that one of skill in the art would clearly understand what is meant by a poly-Ig receptor. However, as stated in the above rejection, the recitation of poly-Ig receptors and Fc receptors encompass defective and variant receptors and there is no nexus between the description of a wild-type or non-defective receptor and a defective or mutant receptor.

Applicant argues that the skilled artisan could easily engineer a mutant version of the poly Ig receptor. This has been considered but not found persuasive. The written description requirement is separate from the enablement requirement. The rejection was not based on undue experimentation so applicants allegation that one of skill in the art could easily construct such a mutant receptor fails to overcome the instant rejection.

Applicant argues that Lily and Enzo are inapplicable in this situation because the poly Ig receptors are known in the art. . Again, it is reiterated that the claims encompass variant and altered receptors, the sequence of which is not disclosed by the specification.

Applicant provides an excerpt of the specification paragraph 0434 to describe the structural properties of poly Ig receptors. Applicant is reminded once again of the instant rejection which stated that

Claims 8, 9, 10, 11, 13, 14, 17, 19, 67, 72, 80 and 88 contain the limitations of "mediator of immunoglobulin inhibition of steroid hormone responsive cell growth". "defective mediator of immunoglobulin inhibition of steroid hormone responsive cell growth", "a poly-Ig receptor" "an Fc receptor", a "variant Fcgamma receptor", and "altered domain in said poly Ig receptor". The specification states on page 11[0022] that "certain other embodiments of the invention provide a method of detecting a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth that includes detecting a poly-Ig receptor". Thus, claims drawn to an immunoglobulin inhibitor of cell growth comprises a genus of inhibitors which include a poly-Ig receptor but is not limited only to poly-Ig receptors. further, given that the claim limitations require the determination of mediation of inhibition of steroid hormone cell growth , it in concluded that

Art Unit: 1643

claims drawn to poly-Ig receptors and Fc receptors encompass defective and variant receptors which differ in amino acid sequence and function from the wild type receptors.

The instant method claims rely on the identity of variant poly-Ig, variant Fc gamma receptors, variant TGF-beta and genes. The claims are thus drawn to a genus of molecules encompassing mutant, truncated and otherwise variant poly-Ig, Fc receptor proteins and TGF-beta. The claims do not limit the "defect" in terms of specific structural or specific functional characteristics., thus it is not possible to determine if a given protein is member of the claimed genus .

Applicant has provided no argument regarding the written description of the variant and altered proteins or the variant and altered sequences encompasses within the genus of an poly-Ig receptor or Fc receptors.

Claims 8, 67, 68 and 91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a functional poly-Ig receptor, or a functional Fc receptor, does not reasonably provide enablement for a method for the method of detecting non-functional receptors of poly-Tg or Fc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims..

The instant claims are drawn to the detection of receptors mediating steroid hormone responsive cell growth, which is drawn to in part to the detection of functional receptors as well as non-functional receptors

The specification has identified the poly-Ig receptor as the epithelial receptor for IgA and IgM (example 24) and an "Fc-like" epithelial receptor for IgG1 (example 25). The specification has not provided any identity of mutated or otherwise defective poly-Ig receptors or Fc-like receptors. The specification has demonstrated that IgA, IgM or IgG1 can inhibit the growth of steroid dependent cancer cell lines in culture. The specification has not provided any evidence that this phenomenon would not be applicable to normal non-cancerous cells, or that cancer cells in culture or in vivo have defective poly-Ig receptors or Fc-like receptors which cannot mediate the observed inhibition. It is noted that all the cancer cells set forth in specific examples by the specification are inhibited by the immunoglobulins and therefore exhibit functional inhibition of

Art Unit: 1643

steroid hormone responsive cell growth and therefore would not be expected to have defective or decreased poly-Ig or defective or decreased Fc-like receptors. Therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to carry out the claimed methods with respect to the identification of defective poly-Ig receptors or defective Fc-like receptors in cancer cells, because the specification does not provide evidence that said defective receptors exist in cancer cells and one of skill in the art would not know in which cancer cells to find said defective receptors.

Claims 7, 12, in part, 13-15, 17 in part, 18 in part, 19, 69, 71 and 92 are drawn to methods of detecting loss of immunoglobulin regulation of steroid hormone responsive cell growth.

The specification has identified the poly-Ig receptor as the epithelial receptor for IgA and IgM (example 24) and an "Fc-like" epithelial receptor for IgG1 (example 25). The specification has not provided any identity of mutated or otherwise defective poly-Ig receptors or Fc-like receptors. The specification has demonstrated that IgA, IgM or IgG1 can inhibit the growth of steroid dependent cancer cell lines in culture. The specification has not provided any evidence that this phenomenon would not be applicable to normal non-cancerous cells, or that cancer cells in culture or in vivo have defective poly-Ig receptors or Fc-like receptors which cannot mediate the observed inhibition. It is noted that all the cancer cells set forth in specific examples by the specification are inhibited by the immunoglobulins and therefore exhibit functional inhibition of steroid hormone responsive cell growth and therefore would not be expected to have defective or decreased poly-Ig or defective or decreased Fc-like receptors. Therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to carry out the claimed methods with respect to the identification of defective poly-Ig receptors or defective Fc-like receptors in cancer cells, because the specification does not provide evidence that said defective receptors exist in cancer cells. It appears from the evidence presented in the specification, that the cancer cell lines tested are under the control of the receptor which responds to the serum inhibitors. The specification does not provide any objective evidence that cancer cells in vivo are not able to respond to said serum inhibitors, therefore there would be no reasonable expectation of success to screen for defective poly-Ig or defective Fc receptors in cancer cells.



Applicant orders the rejection withdrawn on the basis that the language of “non-functional receptors” is not found in the claims. It is noted that the instant disclosure asserts the presence of the defective mediator of immunoglobulin inhibition of steroid hormone responsive cell growth, a variant Fc gamma receptor and an altered domain in a poly-Ig receptor, applicant is referred to the specification paragraphs 0674, 0675, 0677 and 0802 as support for the interpretation that mutant sequences are included with the recitation of poly-Ig receptor and Fc receptor. Therefore, the instant claims encompass non-functional sequences as mutant sequences would include non-functional sequences.

The rejection of claims 8, 67 and 91 under 35 U.S.C. 102(b) as being anticipated by Harris et al (Am J Pathol, 1981, Vol. 105, pp. 47-53) as evidenced by Cargo et al (Journal of Experimental Medicine, 1978, pp. 1832-1836) is maintained for reasons of record.

Claim 8 is drawn to a method of detecting a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth wherein said inhibition can be reversed by steroid hormone, the method comprising detecting in a mucosal epithelial cell a receptor capable of binding the Fc domain of a dimeric/polymeric IgA or polymeric IgM, wherein a detected receptor is capable of binding the Fc domain of dimeric/polymeric IgA or polymeric IgM is indicative that said receptor is a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth wherein the inhibition is capable of being reversed by said steroid hormone.

Claims 67 and 91 embody the method of claim 8 wherein the poly-Ig receptor is detected.

Harris et al disclose a method for detecting Secretory Component in breast ductal epithelial cells (page 49, Table 1), and breast and ovarian carcinomas (page 50, Table 2). Cargo et al provides evidence that secretory component on epithelial cells is the same as the poly-Ig receptor (page 1832, Title). The property of modulating the inhibition of steroid hormone responsive cell growth would be inherent in the secretory component on the breast cells.

Art Unit: 1643

Applicant has provided extensive arguments regarding the adequate written description of the estrogen binding "activity" citing the specification which describes the function of said "activity". However, there is not support in the specification that about the molecular weight of the activity, or a partial amino acid sequence of said activity. Further, there is no positive evidence that the estrogen binding activity is an estrogen receptor, having all of the activities of an estrogen receptor, such as translocating to the nucleus when bound by estrogen..

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants cancellation of claim 91.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1643

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

4/3/2006

  
KAREN A. CANELLA PH.D.  
PRIMARY EXAMINER